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Role of Myocardial Contrast Echocardiography During Nonsurgical Septal Reduction Therapy for Hypertrophic Obstructive Cardiomyopathy

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Objectives. **This study was undertaken to evaluate the ability of myocardial contrast echocardiography (MCE) to guide the targeted delivery of ethanol during nonsurgical septal reduction therapy (NSRT) and to assess the relation between the MCE risk area and infarct size determined by enzymatic and radionuclide methods.**

Background. **NSRT with intracoronary ethanol is a new promising treatment for patients with hypertrophic obstructive cardiomyopathy (HOCM). Proper localization and quantification of the septal infarct before ethanol injection are highly desirable. MCE can provide accurate delineation of the vascular territory of the coronary arteries.**

Methods. **Twenty-nine patients with HOCM and maximal medical therapy underwent NSRT. The left ventricular outflow tract (LVOT) gradient by Doppler echocardiography at baseline was 53 ± 16 mm Hg (mean ± SD). Before NSRT, MCE was performed in all patients with intracoronary sonicated albumin (Albunex). Diluted sonicated albumin (Albunex) was selectively injected into the septal perforator arteries during simultaneous transthoracic imaging. Immediately after MCE, ethanol was injected into the same vessel. Plasma total creatine kinase (CK), total CK-MB fraction and CK-MB fraction subforms were measured at baseline and serially for 36 h.**

Results. **LVOT gradient decreased to 12 ± 6 mm Hg ($p < 0.001$) after NSRT. Accurate mapping of the vascular beds of the septal perforators was successfully attained in all patients by MCE. Furthermore, the MCE risk area correlated well with peak CK ($r = 0.79$, $p < 0.001$). Six weeks after NSRT, 23 patients underwent myocardial perfusion studies performed with single-photon emission computed tomography (SPECT). Mean SPECT septal perfusion defect size involved 9.5 ± 6% of the left ventricle and correlated well with MCE area ($r = 0.7$), with no statistically significant difference between the risk area estimated by MCE and that by SPECT.**

Conclusions. **Estimation of the size of the septal vascular territory with MCE is accurate, safe and feasible in essentially all patients during NSRT. MCE can delineate the perfusion bed of the septal perforators and can predict the infarct size that follows ethanol injection.**

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Hypertrophic cardiomyopathy is a relatively common cardiac disorder that can cause heart failure, angina, syncope and sudden death. Dynamic left ventricular outflow tract (LVOT) obstruction through asymmetric septal hypertrophy and systolic anterior motion of the mitral vale contributes to these symptoms in many patients with this disease. Patients who remain symptomatic despite optimal medical therapy are left with the options of atrioventricular sequential pacing, surgical myotomy or myectomy (1). However, surgical treatment has its morbidity and mortality (1). Recently, Sigwart et al. (2) and Seggewiss et al. (3) described a nonsurgical approach for hypertrophic obstructive cardiomyopathy (HOCM), with intracoronary ethanol injection into the septal arteries, and reported a significant reduction in the outflow gradient (3,4), thus avoiding the risks of open heart surgery. Because the septum is perfused through a number of septal perforators, with significant individual variation and overlap in distribution, exact delineation of the vascular bed perfused by each perforator artery is important to determine the vessel or vessels that should receive the ethanol injection. This targeted delivery of ethanol to induce a localized selective infarction of the hyper-

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Abbreviations and Acronyms

CK = creatine kinase
HOCM = hypertrophic obstructive cardiomyopathy
LAD = left anterior descending coronary artery
LVOT = left ventricular outflow tract
MCE = myocardial contrast echocardiography (echocardiographic)
NSRT = nonsurgical septal reduction therapy
SPECT = single-photon emission computed tomography (tomographic)

trophied septal segment responsible for the outflow obstruction should optimize nonsurgical septal reduction therapy (NSRT) and possibly minimize the risk of complete heart block. Sonicated albumin, an echocardiographic contrast agent, has rheologic characteristics similar to that of red blood cells (5), with a strictly intravascular distribution and can provide quantitative assessment of the extent of myocardium supplied by each septal perforator. Accordingly, myocardial contrast echocardiography (MCE) with sonicated albumin selectively injected into the septal perforator artery can potentially provide an excellent definition of the vascular bed perfused by this vessel and can delineate the area at risk before induced infarction. In this report we describe the use of MCE in patients undergoing NSRT. In addition, the ability of MCE to predict infarct size is compared with cardiac enzyme assays and left ventricular perfusion defects on single-photon emission computed tomographic (SPECT) myocardial scintigraphy.

Methods

Patients. Twenty-nine patients with symptomatic HOCM (4 in New York Heart Association functional class II, 19 in class III, 6 in class IV) receiving maximal medical therapy were enrolled consecutively. The research protocol was approved by the institutional review board of Baylor College of Medicine. All patients provided written informed consent before participation. Subjects had to have evidence of asymmetric septal hypertrophy (basal septal thickness ≥1.5 cm; ratio of septal thickness to posterior wall thickness ≥1.3) with a dynamic LVOT gradient at the site of systolic anterior motion of the mitral valve of ≥40 mm Hg at rest or ≥60 mm Hg during dobutamine challenge (maximal dose 40 μg/kg body weight per min).

MCE studies. Coronary angiography was performed in all patients to exclude significant atherosclerotic coronary artery disease. Projections chosen were those that permitted the best definition of the origin and course of the septal perforator arteries. A 0.014-in. guide wire was then passed into the largest, most proximal septal branch, and a short, small angioplasty balloon (usually 10 × 2 mm) was subsequently advanced over the wire. Before ethanol injection, MCE with intracoronary sonicated albumin (Albunex) was performed. Simultaneous continuous imaging was performed with an Accuson XP-128 ultrasound system with a fundamental frequency of 2.5 MHz using standard views. The apical views (four-chamber and apical long) were selected to allow determination of the spatial extent of myocardial opacification and to determine the outflow gradient by Doppler echocardiography. These views were supplemented in some patients with the parasternal short- and the parasternal long-axis views. The studies were taped on 0.5-in. VHS videotape for subsequent playback and analysis. One to 1.5 ml of sonicated albumin (Albunex) diluted with normal saline (range of dilution 1:3 to 1:1) to optimize myocardial enhancement and minimize attenuation was injected into the central lumen of the balloon, followed by a 3-ml saline flush. After optimization, the gain settings were unchanged. After localization of the area to be infarcted, 2 to 5 ml of absolute ethanol was injected through the central lumen of the inflated balloon. The alcohol was left in place for 5 min. The balloon catheter was then flushed with saline, and the balloon was deflated and removed. Echocardiographic imaging began a few cardiac cycles before contrast injection, through its washout and continuously until the ethanol was flushed. Blood was withdrawn for total creatine kinase (CK), CK-MB fraction and MB isoforms before NSRT and then at intervals until the total CK became normal. Cardiac enzymatic assays were performed using electrophoresis with a technique previously developed and validated at our institution (6).

SPECT myocardial scintigraphy. Six weeks after the procedure, patients underwent stress (exercise or adenosine) thallium-201 SPECT. The SPECT studies were performed using methods previously reported from our laboratory (7). A large field of view rotating gamma camera with a high resolution parallel-hole collimator was used. Thirty-two frames were acquired over a 180° arc. The images were reconstructed using a filtered back-projection algorithm and Butterworth filter with a cutoff frequency of 0.5 Nyquist and an order of 5. Reconstructed tomograms were then reoriented in the standard short-, horizontal long- and vertical long-axes for interpretation and quantitation. Thallium-201 images were quantitated by experienced nuclear cardiologists who had no knowledge of any other patient data. Defect size was derived by the polar map method (7). The raw polar maps for each patient were statistically compared with the corresponding normal data bank to determine the left ventricular perfusion defect size and the extent of scar and ischemia, if present.

Echocardiographic analysis. Echocardiographic analysis was performed off-line using a Digisonics work station (EC500) equipped with Doppler and two-dimensional analysis software by an observer blinded to the CK levels and the nuclear data. Continuous wave Doppler was used to assess the LVOT gradient using the modified Bernoulli equation before and after ethanol injection in the catheterization laboratory (8). The length of the septum opacified by MCE was measured from the long axis of the left ventricle and expressed as a percentage of the septal length from base to apex. The left ventricle was divided into the 16 segments according to the American Society of Echocardiography, where the anterior septum has three segments. The risk area size by MCE (percent of total left ventricle) was calculated as the length of the septum opacified by MCE divided by total septal length

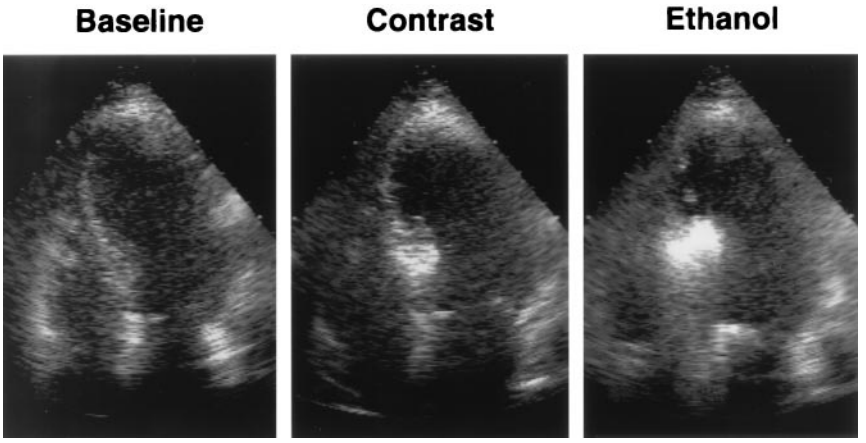


Figure 1. MCE of the septum at baseline and after injection of sonicated albumin (Contrast) and ethanol. Injections were into the first septal perforator. The contrast effect with ethanol has the same distribution as that of the sonicated albumin.

multiplied by 3/16. In addition, the opacified area of the septum in the apical views was planimetered. Subsequently, the area of the septum opacified by ethanol was planimetered.

Statistics. Continuous data are presented as mean volume ± SD. A two-tailed paired *t* test was used to compare the LVOT gradients at baseline and after ethanol injection in the catheterization laboratory. A two-tailed paired *t* test was also used to compare the MCE risk area (percent of total left ventricle) and the SPECT perfusion defect. Linear regression analysis was used to correlate each of the MCE absolute and relative risk areas (percentage of the left ventricle) with peak CK, perfusion defect by SPECT and the septal area opacified by ethanol. Regression analysis was also used to correlate the MCE measurements with the reduction in the left LVOT gradient. Kappa statistics were used to evaluate the agreement between MCE and SPECT with respect to the extent of septal infarction. A p value ≤ 0.05 was considered significant.

Results

Patient characteristics. The mean age of the 29 patients enrolled was 54 ± 15 years (range 31 to 83; 14 men, 15 women). All patients had dyspnea, angina or syncope, and all were receiving beta-adrenergic blocking agents or calcium channel antagonists, or both. All patients had rest dynamic gradients, except for four patients who had only provocable gradients with dobutamine infusion. The mean gradient at baseline was 53 ± 16 mm Hg, which decreased to 12 ± 6 mm Hg ($p < 0.001$) immediately after ethanol injection.

Clinical outcomes. Six weeks after the procedure, the mean rest LVOT gradient was 9 ± 20 mm Hg ($p < 0.01$), and 25 patients were functional class I, and 4 were class II, with only 4 still receiving medications. All patients had transient chest pain during the procedure. The mean hospital stay was 3.6 ± 1.7 days, and although 10 patients developed complete heart block after the procedure, only 8 were pacemaker dependent at 6 weeks. There were no episodes of sustained ventricular tachycardia or ventricular fibrillation. There were no deaths during the procedure or at follow-up.

MCE during NSRT. All patients tolerated sonicated albumin (Albunex) injections without hemodynamic or allergic reactions and without rhythm disturbances. Figures 1 and 2 show myocardial opacification using sonicated albumin in two patients. In all patients MCE localized the septal territory and ensured that balloon inflation prevented retrograde spillage into the left anterior descending coronary (LAD) artery because the septum was the only opacified wall. In one patient with an aberrant origin of a septal perforator from a diagonal branch of the LAD, the opacification of the lateral wall in addition to the septum precluded ethanol administration. Once septal localization was attained and the culprit septal segments were opacified with MCE, ethanol was injected.

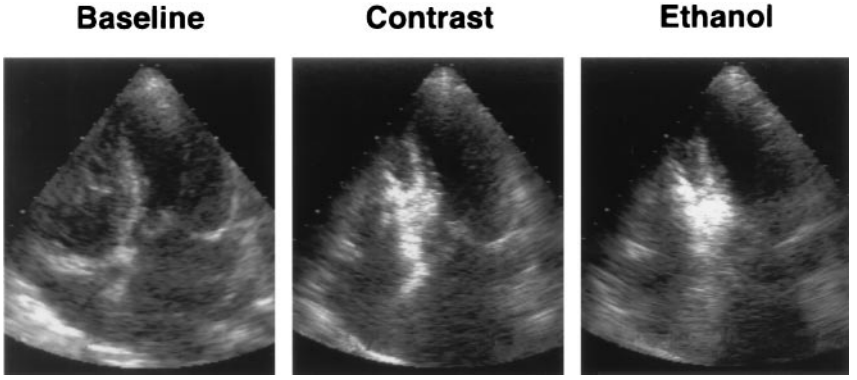


Figure 2. MCE of the septum at baseline and after injection of sonicated albumin (Contrast) and ethanol in another patient. Injection was into the second septal perforator. Note the opacification of the entire septal thickness with both contrast agents.

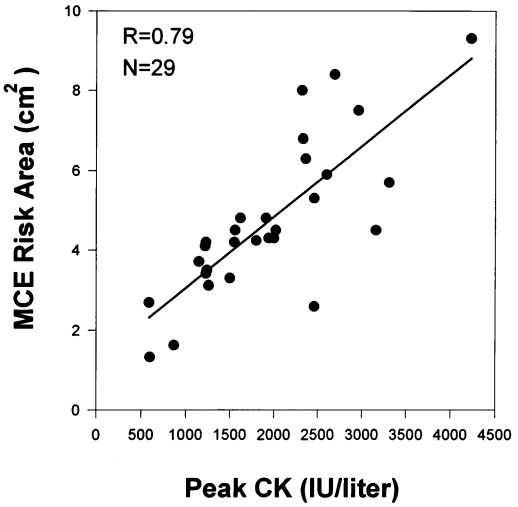


Figure 3. MCE risk area versus peak CK levels in 29 study patients.

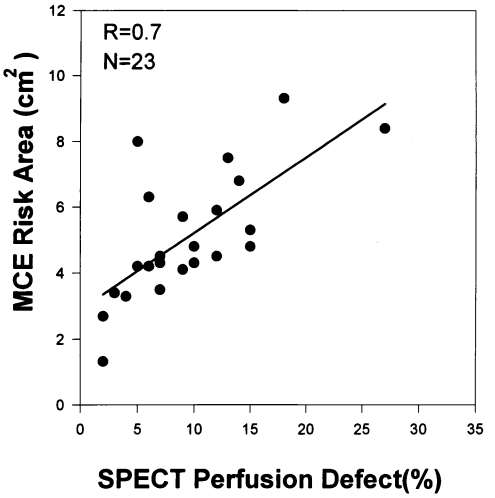


Figure 4. MCE risk area versus SPECT perfusion defects in 23 study patients.

Ethanol was not delivered to the cannulated artery if that artery did not supply the septal segments causing the LVOT gradient. Ethanol injection resulted in a significant contrast effect that was even brighter than that achieved with sonicated albumin (Fig. 1 and 2). The ethanol-opacified myocardial territory was identical to that delineated by sonicated albumin ($r = 0.95$, SEE 0.06, $p < 0.001$). The LVOT dynamic gradient was then measured again by Doppler echocardiography. If the gradient did not resolve, or if there was partial opacification of the segments responsible for the obstruction, the second largest septal perforator was cannulated. Sonicated albumin was again injected into this artery to determine the myocardial bed and in four patients revealed an overlap with the bed of the proximal vessel. Opacification of the proximal septum was observed in 22 patients, and both the proximal and mid segments of the septum were opacified in 7.

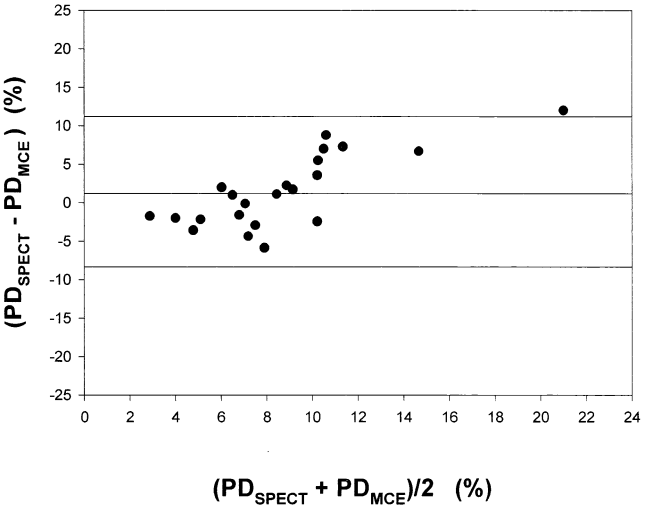
MCE and peak CK. Mean peak plasma CK was 1,937 ± 848 IU/liter (range 591 to 4,230). On average, 33% of the septum was opacified (range 20% to 61%), with a mean area of 4.6 ± 1.9 cm^2 (range 1.32 to 9.3) corresponding to 7.8 ± 2% of the left ventricle (range 3.7% to 11.5%). Significant correlations were present between each of the relative and absolute risk area by MCE and peak CK (area percent: $r = 0.65$; absolute area: $r = 0.79$, $p < 0.001$ for both) (Fig. 3). Patients with a larger reduction in outflow gradient had a greater area of myocardial opacification by MCE (contrast area vs. gradient reduction: $r = 0.48$, $p = 0.012$)

MCE and perfusion defects by SPECT. Twenty-three patients had SPECT studies at 6 weeks after NSRT. The other six patients refused to undergo stress testing. The stress modality was exercise in 20 patients and adenosine in 3. Fixed perfusion defects were present in all patients. Thirteen patients had proximal septal defects, and 10 had defects beyond the proximal septum. There was 87% agreement in the localization of perfusion abnormalities in the septum between MCE and SPECT (kappa 0.72). Mean defect size by SPECT was 9.5 ± 6% (range 3% to 27%), similar to that obtained by MCE ($p = 0.12$). Significant correlations were present between MCE risk area and nuclear SPECT perfusion defect size (MCE area percent: $r = 0.54$, $p = 0.02$; absolute area: $r = 0.7$, $p = 0.001$) (Fig. 4). The Bland-Altman plot of the SPECT and MCE perfusion defects is shown in Figure 5; the mean difference was 1.5 ± 4.6%.

Discussion

NSRT is a promising novel treatment for HOCM. Because it is desirable to limit the ethanol-induced infarction to the septal segments causing the obstruction and to estimate the planned infarct size, we used MCE in the present study. In our preliminary series, MCE successfully mapped the myocardial bed of the cannulated septal arteries and predicted the size of

Figure 5. Plot of the difference between SPECT and MCE perfusion defects (PD) versus the average of both observations.



the ensuing infarction with good accuracy when compared to cardiac enzymes and nuclear perfusion defects.

Role of MCE during NSRT. In each case, MCE confirmed the correct cannulation of the septal perforators of the LAD and their occlusion by the angioplasty balloon without retrograde spillage. In some patients with an anomalous origin of the septal perforators, definition of the myocardial distribution of these arteries during NSRT becomes exceedingly important to avoid the potential for inducing infarction in other regions. Determination of the myocardial distribution of the septal perforators is particularly important because of poor angiographic resolution of the microcirculation and frequent overlap in the distribution of the septal arteries. We noted a significant, albeit only moderate, correlation between the MCE septal area and the reduction in LVOT gradient. In general, when larger sections of the septum were infarcted, there were large decrements in the outflow gradient. However, because ethanol injection was directed mainly to the portion of the septum causing the obstruction, many patients had small defects with a large reduction in the gradient. Targeted delivery of ethanol is of great potential importance in view of the detrimental effects of large infarctions on left ventricular function and the subsequent risks of ventricular arrhythmias and complete heart block. MCE thus successfully guided NSRT to induce the most effective septal infarction.

MCE risk area and prediction of infarct size after NSRT. Previous studies in animals with myocardial infarction induced by coronary occlusion showed that the risk area estimated by MCE correlated with the extent of myocardial necrosis (9–11). In these experiments, the contrast defect by MCE correlated well with the infarct size assessed by triphenyl tetrazolium chloride ($r = 0.84$) (9). More recently, intracoronary injection of sonicated ioxaglate in humans with acute myocardial infarction after reperfusion has allowed the prediction of functional recovery (12) and the extent of myocardial necrosis, utilizing the residual contrast defect immediately after reflow. In the present study, to our knowledge the first to use MCE risk area before controlled infarction in humans, we observed a strong relation between the size of the infarction assessed by peak CK levels and MCE risk area. Because the risk area was determined before occlusion of the coronary artery, the size of the resulting infarction can be predicted a priori instead of after its development.

Few studies have compared MCE and myocardial SPECT scintigraphy. Previous work from our laboratory (13) showed that in dogs with transient coronary occlusion, the perfusion defect size correlates significantly with the contrast area at risk ($r = 0.74$). Our study compared in humans the MCE and SPECT defects in the setting of an acute myocardial infarction. Although there was generally good correlation between the two techniques, the extent of spread may limit the prediction of the SPECT defect size in an individual patient. Nevertheless, in general MCE and SPECT appear to have equivalent roles in the determination of risk area in acute coronary syndromes. Our observations also illustrate the potential utility of this technique in planned coronary interventions because the area at risk (positive contrast) before angioplasty can be used to delineate the jeopardized myocardium should acute occlusion develop.

Conclusions. The present study represents an important new application of MCE in the cardiac catheterization laboratory for patients with HOCM and validates the use of MCE risk area during the procedure as a robust measure capable of quantifying the ensuing infarct size.

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